

### REMARKS

Claims 1-50 are pending in the above-identified application. A substitute specification has been submitted in order to correct typographical errors that occurred during translation of the original PCT application, thus no new matter is being introduced by the present amendment.

More particularly, pages 8, at line 21, and page 49, Table 4, are being amended to agree with the exact language of the original PCT application filed in Japanese (PCT/JP2004/019223).

During preparation of the English Translation of the original PCT Japanese application, for filing in the US receiving office, the English Language translators inadvertently corrected errors occurring in the original filed Japanese Language PCT (i.e., PCT/JP2004/019223), **which errors occurred in the paragraph labeled <35-1> at page 8, and the paragraph labeled [0076] at page 49.**

Accordingly, these translational errors have been corrected by way of the submission of the enclosed "Substitute Specification" under the provisions of 37 CFR §1.125, so that a full and correct English Translation of the originally filed specification of the Japanese Language PCT Application PCT/JP2004/019223 is now set forth in the attached "Substitute Specification."

The enclosed Substitute Specification fully complies with the provisions of 37 CFR § 1.125, inasmuch as:

- (1) the substitute specification includes no new matter,
- (2) the substitute specification is submitted with markings showing all the changes relative to the immediate prior version of the specification of record, wherein
  - (i) the text of any added subject matter is shown by underlining the added text,

- (ii) the text of any deleted matter is shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters,
- (iii) the text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived, and
- (iv) an accompanying clean version (without markings) is being supplied.

**For the Examiner's convenience in reviewing the changes made in the substitute specification, also enclosed herewith are pages 8 and 43 of WO 2005/063713 which is the publication of PCT/JP2004/019223 in the Japanese Language.**

In the enclosed page 8 of WO 2005/063713 a handwritten arrow (⇒) points to the paragraph <35-1> and the error in the paragraph is underlined with a handwritten squiggly double line (i.e., reference is erroneously made to <27> instead of <35>).

In the enclosed page 43 of WO 2005/063713 a handwritten notation points out the error in paragraph [0076] and Table 4 thereof (i.e., Table 4 is erroneously the same as Table 5).

As pages 8 and 49 of the instant application are instantly amended, the above errors originally occurring in the Japanese Language PCT Application PCT/JP2004/019223 are fully contained in the attached "Substitute Specification."

Thus, upon entry of the instant amendment, the instant specification will be a true, accurate and complete translation of the original PCT/JP2004/019223 specification that was originally filed in the Japanese Language.

**CONCLUSION**

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By 

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**Enclosure:** Pages 8 and 43 of WO 2005/063713 (with handwritten comments).  
Substitute Specification Under 37 CFR § 1.125 (Clean Copy and Marked Up Copy)

シ)-7-メトキシ-6-キノリンカルボキサミド エタンスルホン酸塩の結晶( $\alpha$ )の製造方法;

<34-1> 溶媒がジメチルスルホキシドである<34>記載の製造方法;

<35> 4-(3-クロロ-4-(シクロプロピルアミノカルボニル)アミノフェノキシ)-7-メトキシ-6-キノリンカルボキサミド エタンスルホン酸塩の結晶( $\alpha$ )、溶媒および水を混合することを特徴とする、4-(3-クロロ-4-(シクロプロピルアミノカルボニル)アミノフェノキシ)-7-メトキシ-6-キノリンカルボキサミド エタンスルホン酸塩の結晶( $\beta$ )の製造方法;

⇒ <35-1> 溶媒がメタノール、エタノールまたは2-プロパノールである<27>記載の製造方法;

<36> 4-(3-クロロ-4-(シクロプロピルアミノカルボニル)アミノフェノキシ)-7-メトキシ-6-キノリンカルボキサミド、酢酸およびエタンスルホン酸を混合し、溶解させることを特徴とする、4-(3-クロロ-4-(シクロプロピルアミノカルボニル)アミノフェノキシ)-7-メトキシ-6-キノリンカルボキサミド エタンスルホン酸塩の結晶( $\beta$ )の製造方法;

<36-1> 4-(3-クロロ-4-(シクロプロピルアミノカルボニル)アミノフェノキシ)-7-メトキシ-6-キノリンカルボキサミド、酢酸およびエタンスルホン酸を混合し、溶解させた後、貧溶媒および水を加えることを特徴とする、<36>記載の製造方法;

<36-2> 貧溶媒がエタノールまたは2-プロパノールである<36-1>記載の製造方法;

<37> <1>-<24-2>いずれか1記載の結晶を含有する医薬組成物;

<38> <1>-<24-2>いずれか1記載の結晶を含有する、血管新生阻害作用が有効な疾患に対する予防または治療剤;

<39> <1>-<24-2>いずれか1記載の結晶を含有する血管新生阻害剤;

<40> <1>-<24-2>いずれか1記載の結晶を含有する抗腫瘍剤;

<41> 腫瘍が膵臓癌、胃癌、大腸癌、乳癌、前立腺癌、肺癌、腎癌、脳腫瘍、血液癌または卵巣癌である<40>記載の抗腫瘍剤;

<42> <1>-<24-2>いずれか1記載の結晶を含有する血管腫治療剤;

## 5. 水分含量測定

第14改正日本薬局方の一般試験法に記載された水分測定法(B-318~331)に従い、各結晶6~10mgを用いて行った。

[結果]

吸湿性評価の結果を表4~表7に示す。

[0076] (表4) Table 4

メシル酸塩の結晶(C)の吸湿性評価

条件	水分含量	結晶形
初期状態	0.7	C
a-1	0.6	C
b-1	0.7	C

same table

[0077] (表5) Table 5

メシル酸塩の結晶(C)の吸湿性評価

条件	水分含量	結晶形
初期状態	0.7	C
a-1	0.6	C
b-1	0.7	C

[0078] [表6]

メシル酸塩の酢酸和物の結晶(I)の吸湿性評価

条件	水分含量	結晶形
初期状態	2.9	I
a-1	0.6	C
b-1	0.8	C

[0079] [表7]

エシル酸塩の結晶( $\beta$ )の吸湿性評価

条件	水分含量	結晶形
初期状態	1.7	$\beta$
a-1	1.7	$\beta$
b-1	1.4	$\beta$

[0080] メシル酸塩の結晶(A)、メシル酸塩の結晶(C)およびエシル酸塩の結晶( $\beta$ )に関しては、水分含量に顕著な変化はなく、吸湿性は認められなかった。また、外観の顕